IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

RENNER *et al.*

Appl. No. 09/275,883

Filed: March 25, 1999

For: **Inducible Alphaviral Gene Expression System**

Confirmation No.: 1349

Art Unit: 1635

Examiner: Schnizer, R.

Atty. Docket: 1700.0020001/JAG/FRC

Declaration of Sondra Schlesinger Under 37 C.F.R. § 1.132

Commissioner for Patents
Washington, D.C. 20231

Sir:

I, the undersigned, Sondra Schlesinger, declare and state that:

1. I am currently a Professor Emeritus of Microbiology at Washington University School of Medicine, 660 S. Euclid Avenue, St. Louis, MO 63110. A copy of my *curriculum vitae* is attached hereto as Exhibit 19.

2. I have read and am familiar with the above-captioned patent application, including the specification, drawings and claims therein.

3. I have read and am familiar with the Office Action issued on May 3, 2002 (PTO Prosecution File Wrapper Paper No. 22), in which claims 75-79, 81-84, 86-101, 103, 105-107 and 109-136 were rejected under 35 U.S.C. § 112, first paragraph, for insufficient written description and lack of enablement.

4. It is my belief that a person skilled in the fields of molecular biology and virology, upon reading the specification of the above-captioned patent application, would readily be able to obtain additional temperature-sensitive, non-cytopathic alphaviral

replicases without the need to predict the effects of individual or combined mutations on replicase function.

5. It is my belief that, upon reading the specification of the above-captioned patent application, a skilled person in the art would readily be able to obtain additional temperature-sensitive, non-cytopathic alphaviral replicases using an experimental strategy involving mutagenesis and screening. An outline of a screening strategy that would have been contemplated and used by a person of ordinary skill in the art to obtain additional temperature-sensitive non-cytopathic alphaviral replicases is as follows:

(a) subject a nucleic acid molecule encoding an alphaviral replicase to mutagenesis, thereby creating a collection of nucleic acid molecules in which each member of the collection has one or more altered nucleotides relative to the wild-type sequence;

(b) use the nucleic acid molecules obtained in (a) to generate a corresponding collection of virus particles at permissive temperature;

(c) test the virus particles obtained in (b) for: (i) the ability to replicate at elevated temperatures; and (ii) the ability to persistently infect a host cell; and

(d) select virus particles that are unable to replicate at elevated temperatures and that are able to persistently infect a host cell, thereby identifying the nucleic acid molecules of (a) that encode a temperature-sensitive, non-cytopathic alphaviral replicase.

6. The process of subjecting a nucleic acid molecule encoding an alphaviral replicase to mutagenesis could be accomplished by random mutagenesis techniques or site-directed mutagenesis techniques. Both random mutagenesis techniques and site-directed mutagenesis techniques were well known and could have been readily carried out by persons skilled in the fields of molecular biology and virology at the time this application was filed.

7. Nucleic acid molecules encoding alphaviral non-structural proteins that could have been used to produce non-cytopathic, temperature-sensitive alphaviral replicases by mutagenesis would have been readily available to persons skilled in the fields of molecular biology and virology at the time this application was filed.

8. The process of generating alphaviral particles using nucleic acids that encode wild-type or mutant alphaviral replicases was well known and could have been readily carried out by persons skilled in the fields of molecular biology and virology at the time this application was filed.

9. Methods for testing alphaviral particles for temperature-sensitivity and non-cytopathicity were well known and could have been readily carried out by persons skilled in the fields of molecular biology and virology at the time this application was filed.

10. At the time this application was filed, persons skilled in the fields of molecular biology and virology typically engaged in screening methods similar to that which is outlined in paragraph 5 above and, upon reading the present specification, would have been prepared to screen through multiple thousands of candidate particles to identify RNA molecules that contain mutations leading to the desired phenotypes (*e.g.*, non-cytopathicity and temperature sensitivity).

11. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the present patent application or any patent issued thereon.

Respectfully submitted,

Sondra Schlesinger

Sondra Schlesinger, Ph.D.

Date: 03/06/03

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